REMARKS

STATUS OF CLAIMS

Claims 1-57 and 60-65 were pending in the subject application.

Claims 17-24, 27, 28, 47-52, 61-63 and 65 stand withdrawn by the Examiner.

Claims 1, 29, 32, 34-36, 38-40, 42, 44, 46 and 53 are amended.

Claims 58 and 59 stand canceled, without prejudice or disclaimer of subject matter therein, by a previous amendment.

Claims 17-24, 27, 28, 48-52 and 61-65 are canceled, upon entry of the present amendment, without prejudice or disclaimer of subject matter therein.

Accordingly, with entry of this amendment, claims 1-16, 25, 26, 29-47, 53-57 and 60 are pending in the subject application.

STATUS OF AMENDMENTS

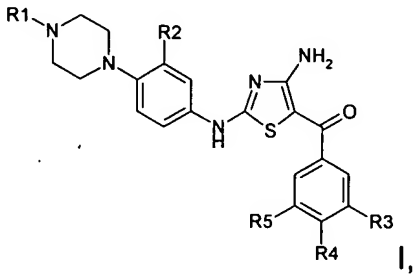
The present amendment is offered to place the application in condition for allowance, or, at least, in better condition for appeal. The claim amendments are offered to more clearly define the subject matter of the present invention. More specifically, the claim amendments are offered solely to either address the issues under 35 USC 112, as further discussed below, or to conform with the Examiner's requirement for restriction, also as further discussed below. No new matter is added.

Upon entry of the present amendment after final, claims 1-16, 25, 26, 29-47, 53-57 and 60 will be pending in the subject application. Without entry of the present

amendment, claims 1-57 and 60-65 will remain pending in the subject application, with claims 17-24, 27, 28, 47-52, 61-63 and 65 being held withdrawn by the Examiner. As can be seen, the present amendment reduces issues for appeal by, *inter alia*, canceling, without prejudice or disclaimer of subject matter therein, the subject matter of the non-elected invention(s).

SUMMARY OF THE INVENTION

The present invention relates to diaminothiazoles of formula



I,

wherein R^1, R^2, R^3, R^4 and R^5 are as described in the specification and claims. These compounds and their pharmaceutically acceptable salts and esters are selective inhibitors of Cdk4. As such, these compounds and their pharmaceutically acceptable salts and esters are anti-proliferative agents useful in the treatment or control of solid tumors, in particular breast, colon, lung and prostate tumors. The present invention also related to pharmaceutical compositions containing the compounds of formula I and their pharmaceutically acceptable salts and esters, as well as intermediates useful in the preparation of the compounds of formula I.

ISSUES

Upon entry of the present amendment, Applicants respectfully submit that the following three issues remain.

First, is the scope of the substituents NR^7R^8, $NR^{12}R^{13}$ and $NR^{15}R^{16}$ definite under 35 USC § 112, second paragraph?

Second, have Applicants provided a disclosure that would enable one skilled in the art to make and/or use the claimed invention as required under 35 USC § 112, first paragraph?

Third, is Applicants' invention non-obvious over the Chong reference (WO 99/21845) under the legal standards of 35 USC § 103?

As will be discussed in more detail below, it is Applicants' position that the answer to each of these three issues must be in the affirmative.

GROUPING OF CLAIMS

With entry of the present amendment after-final, claims 1-16, 25, 26, 29-47, 53-57 and 60 will be pending in the subject application. With entry of the present amendment after-final, claims 1-16, 25, 26, 30, 31, 33, 37, 41, 43, 53-57 and 60 stand or fall together with respect to issue number 1 described above; claims 1-16, 25, 26, 30, 31, 33, 37, 41, 43, 45, 53, 56-57 and 60 stand or fall together with respect to issue

number 2 described above; and claims 1-16, 25, 26, 29-36, 38, 41-46, 53-57 and 60 stand or fall together with respect to issue number 3 described above.

ARGUMENT

Restriction

The Patent Office has made final the requirement for restriction as set forth is Paper No. 5, dated as mailed on June 2, 2003. Applicants respectfully submit that claim 47, indicated as withdrawn from consideration by the Examiner, should be included in elected Group I and considered on its merits. According, Applicants respectfully request reconsideration of the restriction requirement, as it pertains to claim 47, and asks the Examiner for rejoinder and examination of claim 47.

In the spirit of compact prosecution, without acquiescing to the merits of the requirement for restriction, Applicants have cancelled the restricted subject matter as required by the Patent Office (page 3 of the current office action), except for the subject matter of claim 47, for the reasons outlined in the above paragraph. Applicants reserve the right to pursue the non-elected subject matter in one or more divisional applications.

Issue Number 1 : Claim Rejection – 35 USC § 112, Second Paragraph

Claims 1-16, 25, 26, 30, 31, 33, 37, 41, 43, 53-57 and 60 stand rejected under 35 USC § 112, second paragraph, as being indefinite. More specifically, the Examiner asserts that the definition of NR^7R^8, $NR^{12}R^{13}$ and $NR^{15}R^{16}$ are not clearly defined.

The claims, as originally filed, define NR^7R^8, $NR^{12}R^{13}$ and $NR^{15}R^{16}$ as "optionally forming a ring having 5-6 atoms, said ring optionally including one or more additional hetero atoms and being optionally substituted by the group consisting of one of more of OR^6 and lower alkyl which itself may be optionally substituted by OH." While Applicants still believe this language is clear to one of ordinary skill in the art, in order to advance prosecution and overcome the instant rejection, Applicants offer an amendment to this claim language. Specifically, these definitions, upon entry of this amendment, are changed to read "optionally forming a ring having 5-6 ring atoms, said ring atoms comprising, in addition to the nitrogen atom to which R^x and R^y are bonded, carbon ring atoms, said carbon ring atoms optionally being replaced by ~~including~~ one or more additional hetero atoms and said ring atoms being optionally substituted by the group consisting of one or more of OR^6 and lower alkyl which itself may be optionally substituted by OH."

In reviewing the case law cited by the Examiner, (In re Wiggins 179 USPQ 421), this case appears to reject ring-defining claim language on grounds that include the fact that "the claim terminology is so broad that it does not even require that the heterocyclic group contain a carbon atom." Id. at 423. The claims, as amended, now specifically recite that the ring is formed of carbon atoms with one or more optional heteroatoms substituted therein. Support for such an amendment may be gleaned from one or ordinary skill in the art, and, further, in the examples as originally filed, wherein the ring formed may include pyrrolidine, piperidine, and morpholine.

In reviewing the amended phraseology used to define these substituents, Applicants find no language that would inhibit one of ordinary skill in the art to ascertain the scope of these substituents. These groups, such as NR^7R^8, for example, form a

ring having 5-6 ring atoms. This should be clear to one of ordinary skill in the art. The nitrogen atom has two group attached thereto, R^7 and R^8, for example. These two groups, in sum, have 4-5 atoms and form a ring (of 5-6 atoms, total) with the nitrogen atom therebetween. For example, in Example 26, a pyrrolidine group is formed. This may be formed, for example, from R^x and R^y each being an ethylene group ($-CH_2-CH_2-$) joined together at one end, and each joined to the N atom at the other end.

Moreover, applicants' definition of the groups NR^7R^8, $NR^{12}R^{13}$ and $NR^{15}R^{16}$ as optionally forming a ring is well-recognized in the pharmaceutical arts. *See* for example US Pat. Nos. 6,197,804, 6,313,143, 6,313,310, and 6,440,959. For an even broader example, *see* US Patent No. 5,731,299. One skilled in the art clearly understands these terms.

For the totality of the reasons outlined above, Applicants urge that the claims, as amended, are definite under the legal standard of 35 USC § 112, second paragraph. As such, Applicants respectfully submit that the first issue posed be answered in the affirmative, wherein the substituents NR^7R^8, $NR^{12}R^{13}$ and $NR^{15}R^{16}$ are indeed definite under 35 USC § 112, second paragraph. Reconsideration and withdrawal of the instant rejection is respectfully requested.

Issue Number 2 : Claim Rejection – 35 USC § 112, First Paragraph

Claims 1-16, 25, 26, 30, 31, 33, 37, 41, 43, 45, 53, 56-57 and 60 stand rejected under 35 USC § 112, first paragraph as not being enabled. The basis for the rejection is stated in the Office Action dated June 2, 2003: "Such diverse and all encompassing embodiments would not all be expected to show the same activity such as the instantly

disclosed uses – for treating cancer, which is a very structure sensitive art." Office Action at page 7. See also page 4 of the current rejection ("the instant activity is part of a structure-sensitive art as biding to receptor is known to be."). This rejection is again traversed as being scientifically and legally improper.

Applicants submit that the claims are fully enabled in view of the extensive and detailed specification. 35 USC § 112, first paragraph, requires that the specification enable a person skilled in the art to which the invention pertains to make and use the invention. Clearly, the one hundred twenty-four (124) Examples in the specification would be sufficient to teach one of ordinary skill in the art to make the compounds instantly claimed. Moreover, there is no basis on the current record to infer, as the Examiner has done, that one skilled in the art would have any problem ascertaining which compounds within Applicants' defined genus would have antiproliferative activity. On the contrary, Applicants' Example 125 succinctly shows how to test for antiproliferative activity. Therefore, Applicants have taught one of ordinary skill in the art how to use the compounds instantly claimed. Furthermore, Applicants provide, in Table 1, spanning pages 140, 141, 142 and 143 of the originally filed disclosure, IC_{50} data for over 40 of the compounds instantly claimed.

The Patent Office's apparent contention that all compounds embraced by the claims must have the claimed utility for the instant application to be enabled is contrary to legal precedent. It is hornbook law that claims must be interpreted in a reasonable manner and should not be read to include possibly inoperative species. *See, e.g.,* In re Angstadt, 190 USPQ 214, 219 (CCPA 1976); Ex parte Breuer, 1 USPQ2d 1906 (Bd. Pat. Int. App. 1986); and In re Smythe, 178 USPQ 279 (CCPA 1973). The Court's admonitions in In re Smythe are particularly on point. In Smythe the court rejected the

Board's premise that the use of the term "inert fluids" makes the claim so broad as to include inoperable fluids. The court stated:

> [I]t is almost always possible to so construe a claim as to have it read on inoperative embodiments....We therefore cannot agree with the board that the rejection under the first paragraph of § 112 is any more sustainable because the broader term "fluid" includes some "liquids" which might not work. *Id* at 286.

Those compounds within applicants' genera that may not have antiproliferative activity are easily discerned using the disclosed assay of Example 125 (or any of a number of similar art-recognized assays) without undue experimentation. That is all that the enablement requirement of Section 112 requires. *See* Atlas Powder Co. v. E.I. Dupont de Nemours & Co., 224 USPQ 409 (Fed. Cir. 1984). In other words, Applicants have taught one having ordinary skill in the art, how to make and use the claimed invention.

The Patent Office has attempted to distinguish over In re Angstadt and Atlas Powder Co. by stating that in the instant case, "the instant activity is part of a struture-sensitive art as binding to receptors is known to be. Enablement in such cases requires more than in the predictable arts." Office Action at pp. 4-5. Applicants do not dispute that the level of predictability for chemical reactions and physiological activity is different from that of mechanical and electrical elements. However, the very section of the MPEP on which the Examiner relies in support of its position, namely, MPEP 2164.03, merely cautions that in the more unpredictable chemical arts, more than one species may be required. Not unexpectedly, the MPEP does specify what number of species need be exemplified as this is very case dependent. More on point, MPEP 2164.03

states, "In cases involving unpredictable factors, such as ... physiological activity, more may be required.... This is because it is not obvious from the disclosure of one species, what other species will work." (emphasis added). Applicants have given over 40 Examples, spanning several pages of the originally filed disclosure, of the activity of the compounds of the instant invention.

In view of applicants' explicit assertion of utility, the burden is on the Patent Office to present credible scientific evidence supporting its statements that applicants' claimed compounds do not have the stated utility. Mere doubt, without specific scientific evidence or reasons, which is all the current Office Action contains, is not sufficient for maintaining a rejection under 25 USC § 112, first paragraph. In re Marzocchi, 169 USPQ 367 (CCPA 1971), is directly on point. In reversing a rejection under 25 USC § 112, first paragraph, similar to the one pending in the instant application based on the PTO's assertion that the breadth of the claimed terms cover inoperable embodiments, the CCPA held:

> It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *Id.* At 370.

In fact, in In re Fouche, 169 USPQ 429 (CCPA 1971), cited by the Patent Office in support of this rejection, there appears to have been evidence in the record presented by applicants (namely affidavits) that cast doubt on whether certain claimed compounds would have the stated utility. No such evidence exists on the current record. Thus, no basis exists for requiring applicants to provide reasonable

assurances that all compounds will be useful for the described utility. On the contrary, as the CCPA stated in In re Armbruster, 185 USPQ 152 (CCPA 1975):

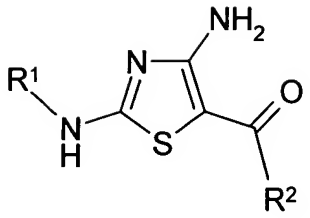
> Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct. Id. at 153.

For the totality of the reasons outlined above, Applicants urge that the claims, as amended, are adequately enabled under the legal standard of 35 USC § 112, first paragraph. As such, Applicants respectfully submit that the second issue posed above be answered in the affirmative, wherein Applicants have indeed provided a disclosure that would enable one skilled in the art to make and/or use the claimed invention as required under 35 USC § 112, first paragraph. Reconsideration and withdrawal of the instant rejection is respectfully requested.

Issue Number 3 : Claim Rejections – 35 USC § 103(a)

Claims 1-16, 25, 26, 29-36, 38, 41-46, 53-57, 60 and 64 stand rejected under 35 USC § 103(a) as being unpatentable over WO 99/21845 ("Chong"). This rejection is again traversed.

Chong relates to compounds of formula



Applicants do not challenge the Examiner's assertion that, by picking and choosing the exact set of variables from a myriad of possibilities in Chong, one may be able to conjure up a compound that, while not specifically disclosed in Chong, falls within the instant claims. Rather, Applicants assert that Chong neither teaches nor fairly suggests the compounds of the present invention.

Under the guidance of In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994), "The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a prima facie case of obviousness." Id. 16 F.3d at 383, 29 USPQ2d at 1552. The prior art must provide some motivation to one of ordinary skill in the art to make the claimed invention in order to support a conclusion of obviousness. See, e.g., In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Examiners are urged to consider the totality of circumstances in making and maintaining obviousness rejections under 35 USC 103. Under this analysis, the Examiners are directed to 1) consider the scope and content of the prior art, 2) ascertain the differences between the prior art and the claims in issue, 3) determine the level of skill in the art, and 4) determine whether one of ordinary skill in the art would have been motivated to select the claimed species or subgenus from the disclosed genus.

The Scope and Content of the Prior Art

As an initial matter, Office personnel should determine the scope and content of the relevant prior art. See, MPEP § 2144.08(II)(A)(1). In the case of a prior art reference disclosing a genus, Office personnel should make findings as to: (A) the structure of the disclosed prior art genus and that of any expressly described species or subgenus within the genus; (B) any physical or chemical properties and utilities disclosed for the genus, as well as any suggested limitations on the usefulness of the genus, and any problems alleged to be addressed by the genus; (C) the predictability of the technology; and (D) the number of species encompassed by the genus taking into consideration all of the variables possible.

Applicants note that it appears the Examiner has at least carried out step (A) from the preceding paragraph, as the Examiner has identified several examples from Chong that are the closest to the genus instantly claimed. These compounds include examples C71, C81, C96, C97, C100, C105, C111, C121, H2, H3, J1, J2 and J3. Each and every one of these compounds have a di-ortho halo substituted phenyl group as the "D" ring of instant claim 1. The "D" ring of instant claim 1 requires hydrogen atoms at both ortho positions, much different from that of the Chong reference. As a matter of fact, in every compound disclosed in Chong that includes ring A as instantly claimed (piperazine), the phenyl ring D always includes a di-ortho-halo (or trimethylfluoro, in one case – example C100) substitution. In light of this observation alone, Applicants fail to see how one of ordinary skill in the art would be motivated to make the compounds instantly claimed, having no ortho-substitution on the phenyl (D) ring. This factor weighs in favor of patentability of the instant claims.

Step (B) in determining the scope and content of the prior art is to determine any physical or chemical properties and utilities disclosed for the genus, as well as any suggested limitations on the usefulness of the genus. At page 10 of Chong, lines 4-5 reads, "...even more preferably, R^2 is such a cyclic ring structure bearing a substituent at the position adjacent or vicinal to the point of attachment (to the core structure)." In other words, assuming, *arguendo*, that one skilled in the art would be motivated to pick and choose a phenyl ring as one of the "carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, ring structure" for which R^2 is so defined, then this phenyl ring is "more preferred" to be ortho-substituted. Chong **teaches away from** using a phenyl ring as the "D" ring (see instant claim 1) that lacks any ortho-substitution. This factor also weighs in favor of patentability of the instant claims.

Step (C) in determining the scope and content of the prior art is to determine the predictability of the technology. At page 4 of the current Office Action, the Examiner asserts that the relevant art is "structure-sensitive art as binding to receptors is known to be." Following the Examiner's very assertion that if the technology is unpredictable, it is less likely that structurally similar species will render a claimed species obvious because it may not be reasonable to infer that they would share similar properties. See, E.g., In re May, 574 F.2d 1082, 1094, 197 USPQ 601, 611 (CCPA 1978). Therefore, this factor also weighs in favor of the patentability of the instant claims.

Finally, Step (D) in determining the scope and content of the prior art is to determine the number of species encompassed by the genus, taking into consideration all of the variables possible. In the instant case, the Chong genus contains an extremely large number of species. The only common core between the structures disclosed by Chong and those of the instant invention is the thiazole ring having an

amine attached to one carbon atom thereof, and a carbonyl attached to another carbon atom thereof. The core of the subgenus of the instant invention is defined by a four ring base structure, thereby significantly reducing the number of possible species of this subgenus as compared to that of Chong. Again, this factor weighs in favor of the patentability of the instant claims.

The Differences Between The Prior Art and The Claims In Issue

In Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1537, 218 USPQ 871, 877 (Fed. Cir. 1983), the Court noted that "the question under 35 U.S.C. 103 is not whether the differences [between the claimed invention and the prior art] would have been obvious" but "whether the claimed invention *as a whole* would have been obvious." (emphasis in original). To ascertain the difference between the claimed invention and Chong, it may be useful to envision the compound as having a left hand side (that defined by rings A and B, as recited in claim 1, or, that to the left of the thiazole ring) and a right hand side (that defined by ring C, as recited in claim 1, or, that to the right of the thiazole ring).

Applicants note that Chong may indeed teach a compound that includes the left hand side of the claimed compound. Additionally, Applicants note that Chong may also teach a compound that includes the right hand side of the claimed compound. However, taking the claimed invention *as a whole*, Applicants urge that Chong fails to teach or fairly suggest the compounds as instantly claimed, with a specifically chosen right hand side and a specifically chosen left hand side.

As discussed earlier, the right hand side of the claimed compounds (the "D" ring of instant claim 1) requires hydrogen atoms at both ortho positions. This differs greatly from that disclosed in the Chong reference. As a matter of fact, in every compound disclosed in Chong that includes the left hand side (rings A and B) as instantly claimed, the phenyl ring D always includes a di-ortho-halo (or trimethylfluoro, in one case – example C100) substitution.

The Level of Skill in the Art

The MPEP suggests that Office personnel should evaluate the prior art from the standpoint of the hypothetical person having ordinary skill in the art at the time the claimed invention was made. While it may be obvious to try the compounds instantly claimed, this is not the correct standard for determining obviousness. It must be obvious, to one of ordinary skill in the art, to make the claimed invention. As previously discussed, in view of the teachings of Chong, it is Applicants' position that one having ordinary skill in the art would not be motivated to make the instantly claimed compounds. More to the point, one having ordinary skill in the medicinal chemical arts would more likely than not be motivated not to make the compounds instantly claimed, as Chong teaches away from the instantly claimed compounds by requiring di-ortho-halo substitution on the phenyl ring when such a ring is present in the structure.

The Motivation to Select the Claimed Species or Subgenus from the Disclosed Species

The MPEP further suggests that Office personnel should determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed

prior art genus. "[A] prima facie case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." In re Deuel, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995) (emphasis in original). As previously discussed, while Chong may separately teach the left hand and right hand sides of the instantly claimed compound, the Examiner must consider patentability of the claimed compound itself, as a whole.

Applicants urge that the Examiner has failed to meet the requisite burden in showing sufficient motivation to modify the reference to come up with the instantly claimed compounds. At the outset, considering the size of the genus of Chong and the relatively (compared to that instantly claimed) small core structure, one of ordinary skill in the art would have to pick and choose the right substituents to arrive at Applicants' core structure.

Assuming, *arguendo*, that one may even accomplish this daunting task to arrive at Applicants' core structure, there remains requisite motivation to choose a "D" ring that has no ortho substitutions. Clearly, Chong fails to motivate a skilled artisan to choose anything but ortho-substituents. As discussed above, every compound disclosed in Chong that includes ring A as instantly claimed (piperazine), the phenyl ring D always includes a di-ortho-halo (or trimethylfluoro, in one case – example C100) substitution. Moreover, at page 10 of Chong, lines 4-5 read, "...even more preferably, R^2 is such a cyclic ring structure bearing a substituent at the position adjacent or vicinal to the point of attachment (to the core structure)." Further, even the broadest claim (claim 1) of Chong limits the ring at the "D"-ring position ("D" referring to the ring shown in the structure as instantly claimed) to having at least one ortho substituent.

In addition to the textual teaching away from any phenyl-"D" ring substitution other than ortho-substitution, the data presented by Chong would also lead a skilled artisan away from the compounds instantly claimed (with no phenyl-"D" ring ortho-substitution). The enzyme data reported in Table I, pages 133- 151, of Chong demonstrate the criticality of having ortho substitution when R^2 is a ring, particularly phenyl. Note, for example, on page 138 the difference in potency between compound C(17) which is ortho substituted (Ki=72 nM) and compound C(18) which is essentially the same as C(17) but is para substituted (Ki=12,900 nM). The ortho substitution yielded a compound that is 179 times more active in the reported enzyme assay than the para substituted compound.

The Examiner urges, at page 6 of the current office action, that "the case law on position isomers previously cited provides ample precedent that position isomers are pirma facie structurally obvious even in the absence of a teaching to modify." (emphasis added). Applicants respectfully submit that this statement is legally improper. In the previous office action, the Examiner points Applicants to MPEP 2144.09. Upon skimming this section of the MPEP, Applicants note the bold face, all capital type stating "Homology and isomerism are facts which must be considered with all other relevant facts in determining obviousness." Moreover, a review of the case law cited by the Examiner reveals that the cases do not appear to boldly hold that position isomers are prima facie structurally obvious even in the absence of a teaching to modify. In Ex parte Engelhardt, 208 USPQ 343 (BPAI, 1980), the Board went through a Graham v. John Deere analysis to arrive an its conclusion. In In re Mehta, 146 USPQ 284 (CCPA, 1965), the Court had two prior art references in front of them, one being a position isomer reference, and the other providing motivation to make the necessary positional change in the primary reference.

For these reasons, as well as what is well-settled legal principle, Applicants urge that, "patent examiners carry the responsibility of making sure that the standard of patentability enunciated by the Supreme Court and by the Congress is applied in each and every case.... Office policy is to follow Graham v. John Deere Co. in the consideration and determination of obviousness under 35 U.S.C. 130." MPEP 2141. By ignoring any finding of motivation to modify, the Examiner appears to be bypassing one of the "basic requirements of a prima facie case of obviousness." MPEP 2143.

The Patent Office persistently maintains that structural isomers are expected to have the same activity and as such, the instantly claimed compounds are prima facia obvious over Chong. However, structural isomers do not necessarily have the same pharmaceutical properties and this "expectation" certainly is rebuttable. *See, e.g.,* T. H. Brown et. al, J. Med. Chem. **1990**, *33*:527-533 and H. Kagechika et al., J. Med. Chem **1988**, *31*:2182-2192 (copies enclosed). In the instant case, the expectation of similar activity for structural isomers is rebutted by the very reference. Chong himself teaches with respect to his compounds, structural isomers in fact do not have the same activity. Chong states and presents evidence that when R^2 is a substituted ring, proximity of the substituent to the point of attachment to the rest of the structure yields better activity. Chong shows that ortho substitution is best, and meta is better than para (*see, e.g.* page 133, compound D(1) which is meta substituted, has a potency of Ki= 490 nM, while the para substituted compound D(2) has a potency of Ki= 5000nM). Chong himself defeats the PTO's prima facie argument.

The PTO mentions that applicants' IC_{50} values and those of Chong are in different units (micro Molar vs. nano Molar, respectively). Applicants are not certain the

point of this statement. Applicants have not argued for a comparison of the CDK4 inhibitory activity of their compounds with those of Chong. Applicants have argued that Chong effectively teaches away from making applicants' compounds which do not have an ortho substituient on ring D. However, since the PTO has raised this issue, Applicants note that their own CDK4 inhibition assay vs. that of Chong are not one in the same, and consequently, one should not necessarily assume that these numbers can be correlated.

In direct contrast to Chong's teachings, Applicants have discovered that their compounds, lacking ortho substitution, are not only highly active, but unexpectedly, are also highly selective. *See* applicants' specification paragraph [0024]. Applicants' compounds are thus not taught or suggested by Chong.

Interestingly, Applicants' claims stand rejected as not being enabled because of the perceived unpredictability in the art. Yet, this very unpredictability is disregarded when finding that Chong obviates the claimed invention. Applicants' concur with the Examiner's interpretation of the law that obviousness does not require absolute predictaility, only a reasonable expectation of success, i.e., a reasonable expectation of abtaining similar properties. Based on the disclosures in Chong, one would expect that non-ortho substituted compounds would be much poorer CDK inhitors.

The PTO requires that to overcome the Chong reference, Applicants must submit comparative data between the instant compounds and the positional isomers of Chong showing unexpected properties. Applicants submit that this request is not proper in view of the current record. The claimed compounds and those of Chong are not merely positional isomers. The Chong genus is very broad and does not otherwise

specifically point to applicants specific compounds. In other words, Applicants' compounds are not merely positonal isomers of the Chong compounds and the PTO seems to contend. For example, Chong's R^1 substituent includes many more options than Applicants' specific dual ring system. Moreover, as mentioned above, Chong himself teaches away from meta and para substituion of R^2 when R^2 is aryl. For these reasons, Chong does not provide the requisite motivation to select Applicants' particular compounds and thus does not render the instant claims prima facie obvious. As such, no comparative data is deemed necessary to overcome this reference.

For the totality of the reasons outlined above, Applicants urge that the claims, as amended, are non-obvious and patentable over Chong under the legal standard of 35 USC § 103. As such, Applicants respectfully submit that the third issue posed above be answered in the affirmative, wherein Applicants' invention is indeed non-obvious over the Chong reference under 35 USC § 103. Reconsideration and withdrawal of the instant rejection is respectfully requested.

Miscellany

At page 4 of the current Office Action, the Examiner states that Reason #6 (of the rejection of the claims under 35 USC 112, second paragraph) remains because no remarks regarding this rejection were made nor any amendment was made to claim 1. Applicants direct the Examiner to the penultimate paragraph on page 50 of the previously filed response (dated as filed on August 8, 2003, Paper No. 6), which states,

> The Patent Office queries applicants' proviso excluding R^4 being Cl when R^3 is $-NO_2$. Applicants are asked whether this was due to prior art

as the Patent Office has not found any art describing such compounds. Applicants concur with Patent Office that these compounds are novel. Applicants' inclusion of this proviso was not due to prior art references, but rather the activity/selectivity of the compounds.

Applicants respectfully submit that the above comments made in the previous response overcome the "rejection" made by the Examiner as "reason #6" (see the Office Action dated as mailed on June 2, 2003, Paper No. 5, at the bottom of page 6). Reconsideration and withdrawal of the same is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the instant application is in condition for allowance. Early notice to that end is earnestly solicited. Alternatively, Applicants request entry of the above amendment as placing the application in better condition for appeal.

If a telephone conference would be of assistance in furthering prosecution of the subject application, Applicants request that the undersigned be contacted at the number below.

No fee is required in connection with the filing of this Amendment. However, if any fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

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